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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,188	02/28/2002	Steven L. Rose	P-PM 4978	8656

23601 7590 05/06/2004

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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/1,188	Rose et al
Examiner	**Group Art Unit**
SAUNDERS	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1-74 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 7, 31, 42-74 is/are rejected.

☑ Claim(s) 1-6, 8-30, 32-41 is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Claims 1-74 are pending and under examination.

The abstract of the disclosure is objected to because the heading "Abstract of the Invention" should, instead, read as—Abstract of the Disclosure--. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: at page 103, line 19 and in Table 8 "Poynard" should be --Imbert-Bismut--. In Table 8, the examiner finds numerous possible misprints. Under the "Prometheus" data:

Is prevalence of ".05979" intended to be --0.5979--?

Is % Equivoc of "03505" intended as--0.3505--?

Is accuracy of ".09113" intended to be --0.9113--?

Under the "Poynard et al" data:

Is % Equivoc of ".0515" intended as -- 0.515--?

Appropriate correction is required.

Claims 1 and 32 are objected to because of the following informalities: In step (a) of each the abbreviation -- (alpha 2-MG)--should appear after "alpha 2-macroghobulin" so that this abbreviation in step (d) is defined. Appropriate correction is required.

All claims depending from 1 and 32 are indicated as objected to.

Claims 7, 31 and 42-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is self-dependent.

In claims 31, 42, 50-53, 61 and 71 "no or mild liver fibrosis" and "moderate to severe liver fibrosis" are relative terms. It is suggested that applicant define these as set forth at specification page 14, line 18-page 15, line 5 and page 16, line 25-page 17, line 3.

In claim 42, last paragraph "remaining individuals" is unclear. The preamble refers to "an individual" singular, but the concluding recitation of "individuals" (plural) implies that a population of individuals is being diagnosed. Likewise, dependent claims 50-53 expressly refer to a "population" of individuals.

Claim 54 is likewise unclear by referring to "an individual" in the preamble and to a "population" of individuals in the concluding paragraph and in dependent claims 62-64.

Claims 65, 72 and their dependents are unclear because they do not recite what the "desired performance characteristic" is and what value it has. As such one does not know where the line of demarcation falls between the assays which are and which are not encompassed by the claims. For example, Table 6 of the disclosure points to the multivariable panels of rows 14-16 as being those that provide the most accurate diagnosis (79.90% or higher). However, if one lowers the "desired" level of accuracy, then any of the tests of rows 3-13 of Table 6 may be encompassed. In the absence of clear metes and bound defining the invention other innovators will be afraid to try new methods involving combinations of variables other than the exemplified alpha-2 MG, HA, TIMP-1 panel. In the absence of clear boundaries, a patent holder would be free to

bring infringement proceeding against any one who conducts further investigations. These scenarios hinder, rather than promote, the advancement of the useful arts and sciences. Therefore the ill-defined claims do not merit patentability in a quid pro quo patent granting system.

As further evidence that mere recitation of "a desired performance characteristic" is indefinite, applicant is referred to Zweig et al (clin. chem. 39, 561, 1993); who teach that various terms reflective of "performance", such as "accuracy", can mean different things to different people (page 561, col.1). With no consistent, art accepted definitions for each of the terms encompassed by "a desired performance characteristic" the metes and bounds of the claimed invention are too fuzzy to meet requirements of 112, second paragraph.

Claims 72-73 are unclear because these recite cut-off values (e.g. x1 and x2) without defining which of these is used to determine whether x is positive or whether x is negative as a marker. Like considerations applies to the cut-offs for variables Y and Z.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has not adequately described the genus of specific binding agents that bind to alpha 2-macroglobulin. Except for applicant's disclosure of antibodies, one of skill could not envision what the other specific binding agents would be like. Applicant has given no structural or physical chemical

characteristics of alpha-2-MG that would permit one to envision what agents, other than specific antibodies, would specifically bind to alpha-2-MG. The specific binding antibodies are not representative of the full range of possible agents that would specifically bind to alpha-2-MG and are, thus, not representative of the genus.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has not adequately described the genus of specific binding agents that bind to hyaluronic (HA). Except for applicant's disclosure of antibodies and of HA-binding protein, one of skill could not envision what the other specific binding agents would be like. Applicant has given no structural of physical chemical characteristics of HA that would permit one to envision what agents, other than specific antibodies and HA-binding protein, would specifically bind to HA. The specific binding antibodies and HA binding protein are not representative of the full range of possible agents that would specifically bind to HA and are, thus, not representative of the genus.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has not adequately described the genus

of specific binding agents that bind to TIMP-1. Except for applicant's disclosure of antibodies, one of skill could not envision what the other specific binding agents would be like. Applicant has given no structural or physical chemical characteristics of TIMP-1 that would permit one to envision what agents, other than specific antibodies, would specifically bind to TIMP-1. The specific binding antibodies are not representative of the full range of possible agents that would specifically bind to TIMP-1 and are, thus, not representative of the genus. It is to be noted that term "specific binding agent" is a term that describes members the genus by function, rather than by structure or by physical/chemical properties. The description must convey what the compound is, not just what it does." Univ. of Rochester v. GD Searle etc. 69 U USPQ2d 1886 at page 1894.

Claims 54-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant was not in possession of the assay method recited in claim 54 and its dependents.

First it is to be noted that claims 54-55 recite a single cut –off value for each variable x, y and z. Applicant's disclosure has shown no method in Example I (using a single cut-off value for each variable shown in Table 5) which results in the recited accuracy of "at least 90%". The results of Example I are set forth in Table 6. Therein the best results obtained with two markers (as required by claim 54) is 79.90% (row 14).

Likewise the best results obtained with three markers are 80.41% and 79.90% (rows 15 and 16 respectively. Further the only result achieved with 4 markers (claim 59) is 77.84% accuracy (row 11) and the only results achieved with 5 markers (claim 60) is 69.5% accuracy (row 10). Thus, with the use of a single cut-off value for each variable (marker), applicant failed to demonstrate any assay having an accuracy of "at least 90%."

The only portion of applicant's disclosure that shows any accuracy results of " at least 90%" is in Table 7; see accuracies listed under "final performance after dual optimization without equivocals" for prevalence rates of 30, 20 and 10 percent (figures set forth therein are consistent with dependent claims 62-64, but examiner has no idea where 40 percent prevalence of claim 54 is shown). It is to be noted that these results of Table 7 are only achieved by using two cut-off points for each marker, according to the dual optimization strategy" of Example II. Applicant was thus not in possession of any test with the recited accuracies of claims 54 and 62-64 wherein only one cut-off was used for each marker.

Furthermore, even if claim 54 were to be limited to an embodiment in which two cut-off values are employed for each marker, applicant would still not have been in possession of what is claimed generically---i.e. generic variables x, y and z. In Example II, the only three variables (markers) which have been subjected to the "dual optimization strategy," employing two cut-off values for each marker, are alpha 2-MG, HA and TIMP-1; applicant has shown no combination of two variables or of any other three which provide for the recited accuracy limit of "at least 90 percent." Since the art

is unpredictable and since one can thus not readily envision what combination of variables, other than those exemplified in Example II , would provide a diagnostic assay having an accuracy" of at least 90%" applicant has not described the genus of assays using generic markers x, y and z. To recite "with an accuracy of at least 90%" is to merely set forth a desired functional characteristic ("performance characteristic") and not what the test is.

Claims 65-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant was not in possession of the genus of diagnostic assays encompassed by claims 65, 72 and their dependents.

Claims 65 and 72 do not recite what the desired performance characteristic is nor what value it may have. As such one cannot envision what assays do and what assays do not belong to the genus of diagnostic assays that are claimed. For example, applicant's disclosure concerning Table 6 appears to point to the multi-variable panels of rows 14-16 as being those that provide the most accurate diagnoses (79.90% or higher). However if one lowers the level of accuracy that may be "desired," then any of the tests described in rows 3-13 of Table 6 could be considered as encompassed by the invention. With an undefined "desired performance characteristic" one cannot readily envision which of the exemplified assay panels do and which do not fall within the

genus, let alone what panels involving un exemplified markers may or may not be encompassed.

Claims 54-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's disclosure has not enabled an assay with the limitations of claim 54 (using only a single cut-off value for each marker) which can achieved the desired performance characteristic of "at least 90%" accuracy.

As noted supra, in the 112 first paragraph lack of possession rejection, applicant disclosed no assay in Example I (using single cut-off values) that provides "at least 90%" accuracy. Applicant did not achieve this desired performance, until he used the dual cut-off value method set forth in Example II.

Likewise, the examiner indicated in the lack of possession rejection, that even with use of dual cut-off value applicant has described no assay which achieved the desired 90% accuracy performance, except in the case in which the variables x, y and z are alpha 2-MG, HA and TIMP-1. Since it is considered that the level of skill in the art is high (Wand's factor D), the level of predictability is low (Wand's factor E) and the quantity of experimentation needed to arrive at the invention would be high (Wand's factor H), applicant is requiring one to conduct undue experimentation in order to reasonably arrive at embodiments other than that exemplified as giving 90% accuracy (Wand's factor G).

Evidence that the level of predictability is low and the quantity of experimentation would be high comes from numerous references of record that teach how, over many years, those of skill have sought for a single marker or combination of markers in a body fluid sample that would provide a reliable method of diagnosing liver fibrosis, apart from evaluation of tissue biopsies. Note Oh et al (Curr Gastroentrology reports, 3, 12, 2001) at page 13, col.2. Likewise note that Gabrielli et al (clin chim acta 265, 21, 1995) teach little diagnostic value is attained by measuring both Laminin P1 and NPⅢ P (page 30).

Note that Castera et al (Jour Hepatalogy) disclose that combining two accurate markers (Laminin and Ⅳ-c) does not improve diagnostic value.

Oberti et al (Gasteroenterology, 113, 1609, 1997), teach that adding other variables to serum hyaluronate "added little information" (page 1615, col.1). Note that Imbert-Bismut et al (Lancet, 357, 1069, 2001) tested 11 markers and picked the best 5 or 6; the performance attained in terms of accuracy seems to be below that required by instant claims 54 and 62-64 (according to applicant's own analysis of "Poynard et al" in instant Table 8). Note that numerous of the 11 markers surveyed by Imbert-Bismut et al (page 1069, col.2) overlap the Markush group of markers suggested by applicant as possibly operable in the instant invention (e.g. claims 3, 5, 35). Applicant is thus asking one to conduct undue experimentation to achieve the accuracies recited in instant claims 54 and 62-64, and whatever he may consider the "desired performance characteristic" of claims 65-66 and 72-73 to be.

Claims 65-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 65, 72 and their dependents lack enablement, because the "desired operating characteristic "is not defined, and its value is not given.

As noted supra (112, second) one does not know what the metes and bounds of the claimed invention may be because the "operating characteristic" is not defined. Likewise, as noted supra (112, first, possession) one cannot envision what the genus of assays may be because the "operating characteristic" is not specified. As such applicant is claiming an invention with an arbitrarily moving boundary. If one does not know what the "desired operating characteristic" may be, one has no idea whether his experimentation has provided an embodiment that is or is not an operative embodiment. Since one is shooting at a moving boundary or target, undue experimentation would be involved in reducing any embodiment to practice, other than what applicant has disclosed in Examples I and II.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 65-66 and 68-71 are rejected under 35 U.S.C. 102(b) as being anticipated by Afdhal et al (Jour Hepatology, 27, 993, 1997).

Afdhal et al disclose that a combination of two urinary markers DES and MP, when level of each is compared to a single cut-off value, provides for a diagnostic method of over 80% accuracy for liver fibrosis; see abstract, in "results paragraph; see Table 4. Since "80%" can be properly taken as "a desired performance characteristic", claim 65 is anticipated.

Furthermore, when the level of a third marker (serum PIIINP) is considered in combination with the above two, diagnostic accuracy improves to 84%. See page 999, col.1 and Table 4. Thus claims 66 and 69-70 are anticipated.

Claim 68 is included because it is not clear from the record as to whether the DOE analysis program used by applicant differs from those used by Afdhal et al (pages 995-996).

Claim 71 is included since "no/mild" vs. "moderate/severe fibrosis" could be interpreted as consistent with the liver fibrosis scouring system used by Afdhal et al (page 996, col.1)

Claims 65 and 71 are rejected under 35 U.S.C. 102(a) as being anticipated by Murawki et al (Jour Gastroenterology, 36, 399, 2001).

Murawaki et al show that a combination of fibrotic serum markers HA and MMP-2 serves to stage liver fibrosis. Their analysis used a single cut-off point for each and calculates specificity and sensitivity. See page 402, col.1.

Likewise they show a combination of HA and PIVNP markers serves to stage liver fibrosis. See page 403, cols 1-2.

Since claim 65 does not recite the nature or the value of the "desired performance characteristic", claim 65 is properly anticipated.

Claims 65 and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Walsh et al (Jour Hepatol, 32, 325, 2000).

Walsh et al disclose that measurements of the levels of serum type IV collagen (IVC) and lamanin each are correlated with the type of liver fibrosis. Walsh et al teach that their diagnostic value is increased when combining both tests (page 329, col.1). Since claim 65 notes nothing about the nature or value of the "desired performance characteristic" anticipation is proper.

Claims 65-66, 69 and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Xuhuai et al (Chinese med. Jour, 110, 198, 1997).

Xuhuai et al teach the combined use of collagen IV and VI (IV - C and VI - C) levels and other markers to diagnosis the progress of liver fibrosis. See abstract-conclusions and page 201, col.1. Since instant claims 65-66 fail to describe the nature of level of the "desired performance characteristic" what Xuhuai et al teach is sufficient for anticipation.

Claims 65-66, 68-69 and 71 are rejected under 35 U.S.C. 102(a) as being anticipated by Imbert-Bismut et al (Lancet 357, 1069, 2001).

Imbert-Bismut et al teach diagnosis and staging of liver fibrosis with 5 or 6 marker panels. See page 1071, col.1-page 1072-col.1 and page 1073, col.1 and following. Accuracy achieved is 89.35%. See applicant's own analysis of "Poynard et

al" in Table 8. Since claims 65-66 recite no quanitative limit upon the "desired performance characteristic" anticipation is properly stated.

Claim 68 is included since it is not clear from the instant disclosures as to how DOE analysis differs from that of Imbert-Bismut et al.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 54-55 and 57-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Imbert-Bismut et al (Lancet , 357, 1069, 2001).

Imbert-Bismut et al's teachings have been noted supra. Their method employs a population having 40.71% prevalence and diagnoses 48.5% of the population with an accuracy of 89.35%. See applicant's own presentation of the data of "Poynard et al" in instant Table 8 (page 104). When applicant adjusts his data (according to an undisclosed calculation or selection of subjects?) to a population prevalence of 40.71%, he diagnoses 68% of the population with an accuracy of 91.13% (lower portion of Table 8 under the "Prometheus" heading; of the two accuracy values, 89.35% of "Poynard et al" and 91.13% of applicant do not appear to have any statistically significant difference. The only difference between the prior art and the claim is that Imbert Bismut et al diagnose Ca 50% of the population while the claim recites 65% of the population.

This difference in the percentage of individuals within the population diagnosed (presumed to be 100% minus the percent of equivocals) is not deemed to constitute a

patentable distinction, because the percentage of equivocals can depend upon the particular nature of the diseased population selected. This percentage can likewise vary with the nature of the assays conducted--e.g. which manufacturer provided the assay kit for a selected marker (e.g. the quality of antibody provided therein). This percentage can likewise vary according to where one draws a cut-off line in the F0 to F4 Metavir fibrosis scoring system; and, also, the stage identified can depend on which pathologist is doing the scoring. Given all of the factors that can affect the percentage of equivocal evaluations, it is reasonably considered that one of skill who repeated the analysis of the 5 or 6 markers taught by Imbert-Bismut et al upon a different patient population and in a different laboratory would find that 65% of the individuals in the population would be diagnosable.

References of interest are the following:

Naveau et al (Dig. Dis. and Sci . 39, 2426,1994) show a diagnosis of liver fibrosis via a PGAA score. This correctly classifies 71% of the patients; as far as the examiner can tell, "correctly classified" is the same as the instantly recited "accuracy" and as Zweig et al's "efficiency". See instant specification page 42 and Zweig et al at page 572.

Fortunato et al (clin chem. 47, 1696, 2001) show diagnosis of liver fibrosis via the use of multivariant analysis. This calculates a score by employing an equation (page 1699, col.1) that combines the values of 6 markers. The calculated score is then compared against a single cut-off value. Thus the level of each marker is not compared against its own cut-off value (x1, y1, z1, etc) as required by instant claims 54+.

Volker et al (WO 01/86304), like Fortunato et al, diagnose liver fibrosis by combining the values of multiple markers in an equation, in order to calculate a single, composite value.

Poynard (6,631,330), like Fortunato et al and Volker et al, diagnose liver fibrosis by combining the values of multiple markers in a function, which calculates a single, composite value.

Claims considered allowable over prior art of record are:

1) Claims 1-53, 56 and 67. No reference teaches the recited combination of markers. The art is deemed to be too unpredictable for one to a priori state what particular combination of markers would be useful.

2) Claims 72-74 no reference teaches the use of a second set (x2, y2, z2) of cut-off values—i.e; "Rule-In/Rule-out Analysis."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is 571-272-0849. The examiner can normally be reached on Monday-Thursday from 8:00a.m to 5:30p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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Saunders/tgd

May 3, 2004

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
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